Cost–benefit analysis of a nationwide inoculation programme against viral hepatitis B in an area of intermediate endemicity

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The large decrease in the cost of vaccines against hepatitis virus B prompts a re-examination of nationwide vaccination campaign strategies. The present study estimates the costs and benefits that would result from a viral hepatitis B prevention programme (with no prior screening) targeted at all under-16-year-olds in Israel in 1990 and only neonates in the period 1991–2034. Israel is situated in an area of intermediate endemicity, where the majority of HBsAg carriers are anti-HBe positive.

Such a policy would reduce the number of cases of viral hepatitis B in the vaccinated cohort from 654 000 to 270 000 over the period 1990–2059, yielding a benefit-to-cost ratio of 1.88: 1 for the health services only. Inclusion also of the indirect benefits of reduced work absences and mortality would increase the benefit-to-cost ratio to 2.77:1. Even when the benefits arising from the reduction in hepatocellular carcinoma and liver transplants were excluded, the benefit-to-cost ratio for the health services alone would still be 1.41:1. The adoption of such a nationwide inoculation policy appears therefore to be not only medically but also economically justifiable.

Introduction

A total of 200–300 million people worldwide are carriers of hepatitis B antigen (HBsAg) (*1–4*). Morbidity and mortality from acute hepatitis virus B (HBV) infection and its sequelae—chronic active hepatitis, cirrhosis, and primary hepatocellular carcinoma (*5–12*)—generate not only considerable direct health care costs (*13, 14*), but also indirect costs in terms of days lost from work (*13*). The cost of hepatitis virus B vaccines has, however, declined rapidly over the past decade from US$ 100 for three paediatric doses (including cold chain and administration costs (*15*)) in 1980 to as low as US$ 2.80 in 1989 for children's doses in some countries.[a] This huge decrease in costs prompted us to re-examine the feasibility of expanding the present policy in Israel of vaccinating against HBV infection only specific at-risk groups, such as Ethiopian immigrants under 2 years of age (*16*) and health service workers, to the nationwide immunization of the entire population aged under 16 years.

Most previous cost–benefit studies of hepatitis B vaccination have either focused on at-risk target populations, such as homosexuals (*14, 17*), hospital staff (*18*), and surgical residents (*14*), or have been confined to neonatal programmes (*19*). Some studies limited their perspective to consideration of benefits in terms of reductions in the number of acute cases, but omitted reductions in chronic sequelae (*17*), or focused only on the impact of programmes on the social security system (*18*). Mulley et al., however, also examined screening followed by vaccination of susceptible persons in the general population (*15*).

The study presented in this article considers all the relevant direct and indirect costs and benefits of a nationwide hepatitis B vaccination programme (with no prior screening) that would be targeted at all under-16-year-olds in Israel in 1990 but only neonates in the period 1991–2034.

Current situation

Notifications

In Israel, an average of 3484 notified cases of HBV infection (0.90 per 1000 population; 55.2%, male) were reported annually over the period 1971–90 (*20–23*). From 1971 to 1986 there were, on average, 13.5 deaths per annum from acute viral hepatitis in the country (*20–23*).

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[a] *Hepatitis B vaccine—attacking a pandemic. EPI Update.* November 1989 (Unpublished WHO document).

Reprint No. **5341**

Initial results from the first 2 months of the newly established system which in January 1992 began reporting hepatitis by type indicate that 17.8% of the reported hepatitis cases in Israel are of type B (*24*), which is considerably lower than that reported in the USA (30.9% in 1987) (*25*). Projections of incidences in the model presented here are based on the average values reported for 1971 to 1990 multiplied by the type B incidence of 17.8%, and adjusted upward because 25–40% of immigrants from the former USSR have been infected with hepatitis virus B prior to their arrival in Israel (D. Shouval, personal communication, 1992).

However, there is considerable under-reporting of hepatitis cases. Estimates of the reporting rates in Israel range from 27% to 60% (*26–30*). For our calculations we used a reporting rate of 33.3%, based on the results of a study that used ambulatory records (*31*), which is similar to the rate (33%) reported for Germany (*32*).

Hospitalizations

The most recent available hospitalization data by diagnosis in Israel are for 1979, when 1288 persons (55.4% male) were hospitalized with a primary diagnosis of hepatitis, with an average stay of 9.7 days (*33*), compared with 9.4 days in 1976 (*34*). The percentage of all notifications that were hospitalized (44.6%) in Israel over the period 1971–80 (*20, 21*) was similar to that reported for West London (48%) (*35*). The combined information from various case studies carried out between 1972 and 1982 in Israel (*36–38*) indicated that the average length of stay for HBV infection was 12.5 days, similar to the 12 days in the USA (*32*) and 12.8 days in England (*17*). In Israel 12.2–28.9% of all cases of hospitalized hepatitis were of type B (*36–40*). Case studies have found a predominance (ranging from 65% (*36*) to 75% (*41, 42*) of males among persons hospitalized for HBV infection.

Methods

A vast array of demographic (age structures and projections, labour force participation), epidemiological (hepatitis incidence and transition probabilities to primary hepatocellular carcinoma), health service (type and amount of care required for cases of HBV infection) and economic data (costs of inoculation, costs of caring for cases of HBV infection) were entered into a computerized spreadsheet model. The major advantage of this approach is the relative ease of adding new information, changing the model specifications, and performing sensitivity analyses.

The cost–benefit analysis model used a methodology developed by Mulley et al. (*15*) and relied sometimes on data adapted from studies in other countries, since not all the relevant data were available for the Israeli population.

The following basic formula was used:

Benefit-to-cost ratio = Benefits of programme/costs of programme

where

Costs of programme = Costs of vaccine
+ labour costs of inoculating
+ training and health education costs
+ transportation costs of vaccine and nurses
+ cold chain costs
+ costs of adverse reactions

and

Benefits of programme = Costs of HBV infection without a vaccination programme
– costs of HBV infection with a vaccination programme

where the costs of HBV infection include those associated with the different stages of the illness, primary hepatocellular carcinoma, as well as of liver transplants.

The following benefit-to-cost ratios were calculated using a 7.5% per annum discount rate and a time horizon of 70 years from 1990 to 2059:

— the direct benefit-to-cost ratio, which only includes costs and benefits that relate to health services (e.g., costs of vaccine, outpatient care, visits to general practitioners, hospitalization, etc.);
— the direct plus work benefit-to-cost ratio, which includes direct costs and benefits in addition to indirect costs and benefits that relate to employment in the national economy (e.g., absence from work because of illness, etc.); and
— the total benefit-to-cost ratio to society as a whole; this includes the direct and indirect work costs and benefits, in addition to those related to the reduction in mortality achieved by implementing the programme.

Cost estimates

Vaccination programme

Vaccine cost. Available hepatitis B vaccines are safe and effective in preventing HBV infection in adults

(*43, 44*), children (*45*), and infants at risk (*46*). The main vaccination strategy would be to inoculate neonates over the period 1990–2034 by triple-dose active vaccination of every newborn, without prevaccination screening of mothers for HBV or passive HBIg vaccination (*47*), since in areas where the majority of $HBsAg^+$ mothers are anti-HBeAg positive there is no need also to provide HBIg (*48, 49*). In addition to the neonatal vaccinations, all persons aged 1–15 years would be targeted for a mass triple-dose vaccination campaign in the initial year.

Perinatal transmission from an infected mother to her newborn varies from 12.5% to 90% depending on the HBeAg status of the mother (*9, 10, 19, 31, 50–55*). A higher incidence of HBV also occurs among children whose mothers were HBsAg carriers at birth (*56*). We assumed a sensitivity of 98% for the HBsAg test and a transmission rate of 16.5%, the mid-point of the 8–25% range for Israel, where approximately 98% of HBsAg carriers are anti-$HBeAg^+$ and less than 10% of $HBsAg^+$/anti-$HBeAg^+$ mothers are also $HBV–DNA^+$ (*55, 57*).

The Israeli population (4 660 200 in 1989) was projected to increase at the 1983–89 geometric growth rate of 1.73% per annum, in addition to the estimated immigration of 900 000 persons from the former USSR and 25 000 from Ethiopia during the 1990s. Projections of the numbers of newborns were based on the 100 757 births in 1989 (*58*), in conjunction with the crude birth rate of 22.10 per 1000 population, adjusted downwards by a factor of 0.1 per 1000 per year to reflect expected demographic changes.

The cost of vaccine was based on an offer by a major drug manufacturer to supply large quantities at US$ 2.19 (including syringes and swabs) per paediatric dose, which is suitable for use on all persons under 20 years of age. The cost of providing three paediatric doses to the estimated 1 569 800 under-16-year-olds who would have been vaccinated in 1990 was US$ 10.44 million (US$ 21.06 million for the period 1990–2034); this includes a provision of 6% for vaccine wastage and a compliancy rate of 95%, similar to that already achieved for poliomyelitis, diphtheria–pertussis–tetanus (DPT), and measles inoculations in Israel (*59*).

Manpower costs. Estimates indicated that more than 270 additional public health nurses would have to be employed to carry out the initial mass campaign; about 30 of them could be retained to work on the neonatal programme over the period 1991–2034.

The manpower costs of the programme in mother and child health centres were estimated to be US$ 4.53 per person targeted (including non-compliers) aged 1–5 years (based on 9 minutes' administration, 15 minutes' vaccination, and 10 minutes' explanation time). For neonates, manpower costs were less (US$ 4.01), since no additional labour costs were attached to the initial vaccination at birth in the hospital.

Because of economies of scale, labour costs were lower than for vaccinations carried out in mother and child health centres, i.e., US$ 2.09 per person targeted for 7–15-year-olds (administration, vaccination, and explanation taking 3, 7.5 and 2.1 minutes, respectively) and only US$ 1.59 for 6-year-olds, since one of the inoculations could be given concurrently with the second dose of measles vaccine.

Health education and training. An allocation of US$ 0.80 per targeted person per year was estimated for health education and training costs: this amounts to US$ 2.52 million (US$ 1.26 million in 1990 alone). Health education will be aimed at raising compliancy levels through public service broadcasts on radio and national and cable television. Training will be directed at increasing the ability of public health nurses to explain to parents and children the reasons for hepatitis B immunization and also raising the nurses' awareness of the importance of following an amended immunization schedule that includes use of hepatitis B vaccine.

Transport costs. Costs of US$ 0.19 and US$ 2.37 per vaccinee were included for the transport of vaccine and nurses, respectively, to schools to permit the vaccinations to be undertaken there. No extra transportation costs are envisaged for the vaccination of under-5-year-olds, since this takes place in mother and child health centres.

Since the vaccination campaign will be carried out in obstetrics departments, mother and child health clinics, day nurseries and schools, no additional transportation costs will be incurred by the inoculated persons in this case.

Cold chain costs. In order to increase the cold chain capacity throughout the delivery system, extra cold chain costs of US$ 500 000 in 1990 would be required to purchase additional refrigerators.

Absences from work. For neonates it was assumed that no parental work losses would occur since the second and third doses could be integrated within existing infant immunization schedules against poliomyelitis. In any case, most previously employed mothers would still be on maternity leave (3 months' paid and up to 1 year unpaid). For children aged 1–5 years, the absence from work by parents (assumed to be female) accompanying their children for vaccina-

tion were calculated using the female age-specific participation rate in the labour force multiplied by the average female wage for an estimated 2.5 hours' absence from work. The mothers of all children aged 1–15 years were ascribed 1.5 days' absence from work for each adverse reaction to care for the child and accompany them to the doctor. No work losses were assigned for the school-based vaccinations, since these did not require the presence of a parent. The loss of schoolwork for each child vaccinated was assumed to have a zero economic cost.

Adverse reactions. Approximately 10% of the vaccinees are expected to report temporary soreness or erythema at the injection site (*32, 43, 60*). In total, minor reactions are expected to occur in 25% of vaccinees (*15*); about 10% of such reactions will result in a visit to a doctor (*61*) costing US$ 4.67 (15 minutes at US$ 16 per hour for the doctor plus 5 minutes at US$ 8 per hour for a secretary (or nurse)). There are no known serious chronic side-effects associated with vaccinating neonates with hepatitis B vaccine (*19, 62, 63*). It was assumed that there would be no serious adverse reactions or fatalities as a result of the vaccination campaign because of improvements in the vaccine since the study by Mulley et al. (*15*), who assumed a fatality rate of 1 per million vaccinations. Adverse reactions (US$ 1.05 million) are expected to account for approximately 2.9% of the total vaccination costs.

Overall costs. The net present value (using a 7.5% discount rate) of costs to the health services of the whole programme over the period 1990–2034 was estimated to be US$ 36.7 million (US$ 21.06 million for vaccine costs, US$ 11.06 million for labour costs, US$ 2.52 million for health education, US$ 1.05 million for adverse reactions, US$ 0.51 million for transport, and US$ 0.47 million for cold chain costs). Additional costs of US$ 7.06 million were assigned to cover absences from work as a result of accompanying children for their inoculations in the mother and child health centres, while absences from work to accompany persons with adverse reactions to the doctor were estimated to amount to US$ 1.88 million.

Cost of treating viral hepatitis B

Vaccination will result in a considerable reduction in morbidity and mortality from HBV infection. Since outlays for medication and surgery are usually minimal for patients with HBV infection, and outweigh any increased costs of isolation, the hospital costs were assumed to be only 85% of the average hospitalization fee (US$ 265). The costs of visits, hospitalization, and laboratory tests (obtained from the Ministry of Health and the General Sick Fund, which insures over 75% of the Israeli population) are reported elsewhere (*47*). Table 1 summarizes these costs, by type and stage of HBV infection, as well as the transitional probabilities of developing further stages of the infection, by vaccination status (*15*).

Chronic active HBV infection accounts for 30–60% of cases of cirrhosis in the 20 years following acute infection (*56, 64, 65*). Rapid death from fulminant hepatitis (median age of death, 45 years (*15*)) incurs US$ 8341 in health care costs for only 7 days in an intensive care unit (US$ 1192 per day, 4.5 times the average daily hospital fee). Mortality costs of US$ 130 404 (assuming that the proportion of males who die is the same as that of male HBV infection notifications) were estimated for fulminant hepatitis using the gross national product (GNP) per head method, which assigns an equal value to everyone in society, equivalent to the GNP per head of the population, based on discounting the value of the deceased person's expected years of life lost (*66*).

The cost of each stage of HBV infection was multiplied by its probability of occurrence to calculate the average cost per case. Because of the assumed greater severity of hepatitis in an unvaccinated patient (*15*), the average direct cost was nearly 3.5 times that of a nonresponding vaccinee (US$ 711 versus US$ 207).

Table 1: **Direct costs (per case) of viral hepatitis B, by type and stage, in Israel**

Type/stage	Outcome (% of cases): Unvaccinated	Vaccinated	Direct costs (in US$)
Subclinical	50.00	75.00	0
Anicteric	30.00	13.00	477
Icteric	19.90	11.99	888
Non-fulminant	99.90	99.00	
Resolved	89.91	98.01	0
Asymptomatic carrier	4.995	0.495	59
Persistent	3.497	0.347	2111
Chronic active	1.499	0.149	20 176
Fulminant	0.10	0.01	
Resolved	0.0200	0.0020	3672
Asymptomatic carrier	0.0050	0.0005	59
Persistent	0.0035	0.0004	2111
Active	0.0015	0.0002	20 176
Fatal[a]	0.0700	0.0070	8341

[a] In addition there are mortality costs of US$ 130 404.

Cost of work losses

The cost of loss of work for adults with HBV infection in the inoculated cohort was calculated by multiplying the age- and sex-specific labour force participation rates by the age- and sex-specific wage costs (*67*) and the age-specific notification rates (*20–22*). Data were adjusted for the estimated 55.2% of male notifications and an unemployment rate of 11.0% (the rate expected for 1992 in Israel).

Since no data for Israel were available on absences from work arising from HBV infections regardless of etiology, we used Adler's estimate for England (*17*) of 117.3 days per year, adjusted upward to 123.2 days per year to reflect the 5.5 days' working week of approximately half the Israeli workforce. This estimate was applied to each stage of HBV infection, except the subclinical and fatal fulminant forms. The fatal fulminant form was estimated to cause 20 lost work days before death. Working parents (assumed to be females aged 18–34 years) were estimated to be at home for 30 days to care for their unwell children.

Benefits

We assumed that the incidence of HBV infection among vaccinees and the transmission rate from mothers to neonates would fall by 95% (the efficiency rate for the vaccine) during the first 5 years following vaccination (*43, 68, 69*). A study of widespread use of hepatitis B vaccine in remote Eskimo villages has reported a decrease in the incidence of HBV transmission of 99% over a 5-year period in persons of all ages (*70, 71*).

Since no data are available on the effectiveness of the vaccine for longer periods, we assumed that its efficiency would fall by 15% every 5 years, i.e., to 80.75% (95% x 85%) after 10 years, to 68.64% (95% x 85% x 85%) after 15 years, etc.

If it is assumed that the rate of compliance is 95% (*59*), the number of cases among the inoculated cohorts would fall from 1617 to 61 in 1990 and from 10 081 to 2213 in 2034. In addition to a decrease in the absolute number of cases, the case mix of HBV infection and its complications will become less severe as a result of vaccination (*15*).

The main monetary benefits of hepatitis vaccination is the cost averted in caring for a reduced number of cases. Reductions in incidence were multiplied by the population estimates, and the product obtained was multiplied by the relevant unit cost per case, depending on vaccination status (Table 1). Direct, work, and mortality costs were calculated for the 2.5% of individuals with HBV infection who were expected to develop primary hepatocellular carcinoma and die from this condition (*72*) at either a mean age of 45 years or 64 years, depending on their mothers' HBeAg status (*73*).

Our estimates of the costs associated with chronic active hepatitis are 11.2% higher than those reported by Arevalo & Washington (*19*), who calculated care costs of US$ 41 453 per case (at 1990 price levels) for this condition, all falling in the 44th or 64th year of life. Mortality costs of US$ 130 404 were estimated for chronic active hepatitis using the GNP per head method of valuing life for those who died aged 45 years and US$ 94 697 for those who died aged 64 years.

The estimates of liver transplant costs were based on a projection that 7.5% of persons with chronic hepatitis will require a liver transplant at an average age of 42 years. It was assumed that 10% of such transplants would be performed in Israel (each costing US$ 43 506)[b] and the remainder in Europe (cost, around US$ 87 000 for the operation and a further US$ 7400 for air travel, accommodation, and accompanying doctor). In addition, it was assumed that all transplant recipients required medication costing around US$ 10 000 per year for 7.5 years after the transplant. A further US$ 36 400 was estimated for work losses of 1.5 years for patients and 1 year for their spouses.

Cost–benefit analyses

Implementation of the nationwide vaccination policy would reduce the number of cases of HBV infection in the vaccinated cohort from 654 055 to 269 779 over the period 1990–2059. This would be associated with an attendant decrease in mortality, and generate benefits of US$ 68.8 million from reductions in the use of health service resources (costs, US$ 36.7 million), yielding a benefit-to-cost ratio of 1.88:1 (Table 2). Inclusion also of indirect benefits and costs of work absences increases the benefits to US$ 142.6 million and the costs to US$ 45.6 million and gives a benefit-to-cost ratio of 3.13:1. Addition of averted mortality costs increases the benefits to US$ 162.6 million and the benefit-to-cost ratio to 3.57:1. The internal rate of return of the project is 11.3% per annum, which represents the discount rate at which benefits are exactly equal to costs.

Exclusion of benefits from reductions in the costs of primary hepatocellular carcinoma and liver transplants reduces the benefit-to-cost ratios to

[b] [*Hospitalization prices from 1.1.92, No. 24/91*]. Ministry of Health, Jerusalem, December 1991 (in Hebrew).

Table 2: **Cost–benefit analysis of hepatitis B vaccination of under-16-year-olds in Israel**

	Direct	Direct and work	Direct, mortality, and work
	(in US$ millions)		
Vaccination costs	24.6	31.6	31.6
Labour costs	11.1	11.1	11.1
Adverse reactions	1.0	2.9	2.9
Total costs	36.7	45.6	45.6
Hepatitis costs without vaccination	63.3	267.5	275.7
Hepatitis costs with vaccination	11.5	148.7	149.5
Benefits	51.9	118.9	126.1
HCC[a] costs without vaccination	18.7	38.5	120.7
HCC costs with vaccination	15.8	32.8	102.2
Benefits	2.9	5.7	18.5
Transplant costs without vaccination	93.1	119.3	119.3
Transplant costs with vaccination	79.1	101.3	101.3
Benefits	14.1	18.0	18.0
Benefit-to-cost ratio	1.88	3.13	3.57

[a] HCC = primary hepatocellular carcinoma.

1.41:1 (direct costs only), 2.61:1 (direct and work costs), and 2.77:1 (direct, work and mortality costs).

Discussion

In Israel, where the risk of developing HBV infection during a lifetime is intermediate, an estimated 2.0–2.5% of the population are carriers (depending on the mix of ethnic backgrounds), i.e., 2000–2500 babies annually are at risk of acquiring HBV infections from vertical and horizontal transmission. In addition, there are currently around 70 000 HBsAg carriers in the general population who can transmit the disease horizontally. Since 98% of carriers in Israel are anti-HBe positive (of whom 6–8% still have circulating HBV–DNA (*68*)), the magnitude of the problem is less than that in the Far East or Africa, but is still greater than that in Western Europe or the USA.

By February 1992, approximately 35 countries, primarily in eastern and southern Asia, the Pacific Basin, and the Middle East, had a national policy of hepatitis B immunization of newborn children (*74*). If Israel were to introduce not only a national neonatal hepatitis B vaccination policy (*47*), but also a policy of vaccinating children under 16 years of age, the net savings in direct health service costs (i.e., benefits minus vaccination costs) in the period 1990–2059 would be US$ 32.2 million (US$ 15.2 million if primary hepatocellular carcinoma and liver transplant costs are excluded). If work absences and mortality costs are included in the analysis, the programme would save the country around US$ 117.0 million (US$ 80.5 million excluding primary hepatocellular carcinoma and liver transplant costs).

Table 3 shows the results of a sensitivity analysis for various discount rates, reporting rates, and vaccine costs. Vaccination should programme the immune system "memory" of vaccinees and any further encounter with hepatitis viruses should result in an anamnestic reaction. This effectively reduces the vaccine decay rate to 0%, and the vaccine's efficacity should remain at 95% throughout the person's lifetime. The benefit-to-cost ratios were insensitive to changes in both the vaccine decay, the rate of compliancy, and the unemployment rate (an increase in unemployment to 15% only decreasing the total benefit-to-cost ratio to 3.53:1).

The direct costs exceeded the benefits only if the reporting rate was 50%, the discount rate 10%, and if the vaccine costs were more than US$ 1.43 per paediatric dose. In all other cases shown in Table 3, the direct (and total) benefits exceed the costs. Even if the reporting rate were as high as 60%, the direct benefit-to-cost ratio (1.04:1) would still be greater than unity. If the cost of vaccines for children were only US$ 0.933 per dose,[c] the total health service costs of the programme would fall to US$ 24.8 million, resulting in a direct benefit-to-cost ratio of 2.77:1 and total benefit-to-cost ratio of 4.82:1.

Theoretically, a booster injection should raise antibody levels to above the threshold level of protection. However there is no unequivocal evidence that the decline in antibody levels below the threshold in a vaccinee who initially seroconverted leads to clinical HBV infection. Also, since most transmissions of HBV in Israel occur at birth or in pre-adolescence, booster doses are less likely to be needed than in countries where transmission among adolescents and young adults occurs sexually or intravenously. Our model is therefore based on the assumption that no booster infections are necessary; nevertheless, we also calculated the benefit-to-cost ratio for a scenario where boosters are given every 5 years up to the age of 15 years. Use of boosters would increase the direct and total costs of the programme to US$ 52.8 million and US$ 61.7 million, respectively, for the period 1990–2034, and thereby

[c] See footnote *b*, p. 761.

Table 3: **Benefit–cost ratios for hepatitis B vaccination campaign, by vaccine cost and by reporting and discount rates**

Vaccine cost (US$ per dose)	Direct costs and benefits at: (US$ million)				Total costs and benefits at: (US$ million)			
	Discount rate (%)[a] of:				Discount rate (%)[a] of:			
	0	5	7.5	10	0	5	7.5	10
1.00	42.10; 28.07	5.03; 3.35	2.70; 1.80	1.74; 1.16	122.97; 81.99	9.70; 6.47	4.73; 3.15	2.92; 1.95
1.40	36.68; 24.45	4.37; 2.92	2.35; 1.57	1.51; 1.01	108.71; 72.48	8.69; 5.79	4.25; 2.84	2.63; 1.76
1.70	33.55; 22.30	3.98; 2.66	2.14; 1.43	1.38; 0.92	100.01; 66.68	8.05; 5.37	3.96; 2.64	2.46; 1.64
2.00	30.74; 20.49	3.66; 2.44	1.97; 1.31	1.26; 0.84	92.60; 61.74	7.51; 5.01	3.70; 2.47	2.31; 1.54
2.17	29.36; 19.58	3.49; 2.33	1.88; 1.25	1.21; 0.80	88.79; 59.20	7.22; 4.82	3.57; 2.38	2.22; 1.48

[a] The left-hand and right-hand figures in each pair refer to reporting rates of 33% and 50%, respectively.

decrease the direct benefit-to-cost ratio to 1.31:1 and the total benefit-to-cost ratio to 2.58:1. The internal rate of return of the project would then fall to 9.2% per annum.

Unfortunately no Israeli data are available on the age at onset of the initial HBV infection for age-specific cases of primary hepatocellular carcinoma, an underestimate (or overestimate) of the age of cases producing upwardly (or downwardly) biased benefit-to-cost ratios.

In accord with the conservative nature of our estimates, we omitted the cost of transport and time involved in visiting a hospitalized person in the valuation of benefits. Under the assumption that patients would be well enough to be discharged directly from hospital, no provision was made for convalescence costs. It was also assumed that parents accompanied their children on ambulatory visits outside working hours. No evaluation was ascribed to the benefit of having an increased potential pool of blood donors in the population, since around 1.5% of all blood donations in Israel are disqualified because of their HBsAg positivity (S. Bar-Shani, personal communication, 1991).

Our benefit-to-cost ratios are also biased downwards because we assumed no reduction in the incidence of HBV infection among persons who had never been vaccinated. As a result of herd immunity, such individuals will also experience a reduced incidence of HBV infection, a further benefit of the vaccination programme.

No valuation was put on the intangible benefit of freedom from the anxiety of contracting HBV infection that nonvaccinated persons might experience. Finally, no attempt was made to quantify the benefits (to both the ill person and their relatives and friends) of reduced pain, worry, or grief as morbidity and mortality decrease.

However, the model does have an upward bias because some individuals aged 1–15 years might have already been infected with HBV, especially in the early years of the programme. The only data available for Israel (*75*), based on a sample size too small to be generalizable, show that the majority of infections are acquired horizontally among 6–10-year-olds. This and the inverse relationship between the risk of becoming a chronic carrier and the age at infection (*71*) promote an upward bias in the estimated number of cases prevented by the programme.

Implementation of the programme (among 0–15-year-olds in Israel) would result in 384 000 fewer cases of HBV infection over the period 1990–2059. This considerable decrease in morbidity could be gained at no net cost to society; indeed, a net saving of around US$ 124.0 million would accrue. Approximately US$ 32.2 million of this will be savings to the health services, sufficient to finance, e.g., over 850 heart transplants, 1300 kidney transplants, 1700 bone marrow transplants, 3700 coronary bypass operations, or over 8700 balloon angioplasties. No barrier to the implementation of such a programme should therefore be presented by health service agencies provided they retain a long-term budgetary perspective. Even if the Ministry of Health is unable to provide funding, private insurance funds would do well to initiate such a programme on their own, since they would save approximately US$ 320 000 for each percent of the population that was covered. However, this is unlikely to occur since in Israel insurance funds generally hold the attitude that the cost of preventive inoculations should be borne solely by the government public health services. An alternative strategy of levying a user charge to cover the costs of vaccination and side-effects might reduce compliance with the programme.

Approximately 30% of patients with HBV infection do not fall into a defined risk group (*76*). Where risk factors exist, as in the case of health care workers, hepatitis B vaccination programmes have covered less than half of the targeted population

(*77*), despite the assumed high awareness of such a group. As a consequence of the policy in Israel of dispersing new immigrants throughout the entire country after an initial year in an absorption centre, there are no clearly defined neighbourhoods or areas where pockets of HBV infection occur. Therefore any strategy that focuses on high-risk population groups, e.g., those of Ethiopian, North African, Middle-Eastern or Kurdish origin (*78, 79*), will be costly, impractical, and unlikely to produce marked decreases in the incidence of the disease.

The objective of eliminating HBV infection necessitates a new universal vaccination strategy using currently available vaccines. In Israel the benefits of nationwide hepatitis B vaccination in terms of reduced morbidity and mortality justify the expenditures required. In recent years, Israel has introduced routine mumps and rubella vaccinations at 15 months of age (*80*), and use of a second dose of measles vaccine at 6 years of age (*81, 82*). The total benefit-to-cost ratios of these two programmes, determined using a similar methodology to that described here, were 4.2:1 and 5.3:1 respectively, i.e., similar to the ratio 4.22:1 that we calculated for a nationwide vaccination programme against HBV infection.

The vaccination strategy that we have described is valid also for other Mediterranean countries (e.g., Spain, Italy, Turkey, Greece, and Cyprus), where the majority of the carrier population are asymptomatic $HBsAg^+/anti\text{-}HBe^+$. Higher benefit-to-cost ratios would be expected in those countries that are in areas of high endemicity. However, our results cannot be extended to less developed countries whose hospital systems do not provide high-quality, high-cost curative care. Such countries are likely to have far lower direct health care benefit-to-cost ratios, though this may be offset by the greater impact of vaccination in reducing mortality.

The logistical, manpower and cost problems presented by a mass vaccination programme to immunize all 0–15-year-olds in 1 year could be reduced by staggering the programme over a number of years, or by using alternative strategies such as immunizing all neonates plus all 6-year-olds (in a 6-year campaign). Because it has been suggested that in Israel the majority of horizontal transmissions occur in under-13-years-olds (*75*), immunization of a cohort of 6-year-olds would be preferable to a strategy of immunizing an adolescent cohort.

If the cost of a programme covering all under-16-year-olds is prohibitive (US$ 17.8 million for 1990 and US$ 32.2 million in the period 1990–2034), a lower cost option (US$ 1.20 million for 1990 and US$ 21.2 million in the period 1990–2034) aimed at inoculating all neonates (*47*) (with no booster doses) should be considered since this would yield a direct benefit-to-cost ratio of 1.78:1 and total benefit-to-cost ratio of 2.91:1.

In May 1991, partly on the basis of information presented in earlier drafts of this article, the Infectious Disease Committee of the Ministry of Health unanimously proposed the adoption of neonatal vaccinations against HBV infection without prior screening. The vaccination of all newborns nationwide commenced in January 1992. In March 1992, the Infectious Disease Committee decided not to recommend the expansion of the neonatal programme to the other age cohorts.

Acknowledgements

We thank Professor J. Aravelo, University of California, Davis, Sacramento, for his information on costings. The opinions expressed in this article are those of the authors and not necessarily those of the Ministry of Health. This work was supported in part by the S.K. Foundation (Netherlands).

Résumé

Analyse coût/bénéfice d'un programme de vaccination anti-hépatite B à l'échelon national dans une zone d'endémie intermédiaire

L'importante baisse du coût des vaccins anti-hépatite B enregistrée au cours de ces dix dernières années incite au réexamen des stratégies de campagnes de vaccination à l'échelon national. La présente étude fait l'estimation du coût et des bénéfices qui résulteraient d'un programme de prévention contre l'hépatite B en Israël (sans dépistage préalable) ciblé sur tous les moins de 16 ans en 1990, puis uniquement sur les nouveau-nés de 1991 à 2034. Israël est situé dans une zone d'endémie intermédiaire, où la plupart des porteurs de l'HBsAg sont anti-HBe positifs.

La première vaccination devrait conférer une protection à 95% pendant les 5 premières années. Nous avons ensuite supposé que l'efficacité du vaccin diminuerait par la suite de 15% tous les 5 ans (80,75% au bout de 10 ans; 68,64% au bout de 15 ans, etc.).

Le montant net actuel (en prenant un taux annuel d'actualisation de 7,5%) du coût représenté pour les services de santé par l'ensemble du programme entre 1990 et 2034 serait de US $36,7 millions (US $21,06 millions pour les vaccins, US $11,06 millions pour la main-d'œuvre,

US $2,52 millions pour l'éducation sanitaire, US $1,05 million pour les réactions indésirables, US $ 0,51 million pour le transport et US $0,47 million pour la chaîne du froid). Des dépenses supplémentaires de US $7,07 millions seraient encourues en raison de l'absence à leur travail des personnes qui accompagneraient les enfants dans les centres de santé maternelle et infantile pour les faire vacciner et de US $1,88 million pour l'absence à leur travail des personnes accompagnant chez le médecin les enfants ayant des réactions indésirables.

En supposant un taux d'observance de 95% et un taux de vaccins gaspillés de 6%, une telle politique permettrait de diminuer le nombre de cas d'hépatite B dans la cohorte vaccinée, le faisant passer de 654 000 à 270 000 entre 1990 et 2059. En outre, les cas d'hépatite B et les complications seraient moins sévères du fait de la vaccination; le coût direct estimé moyen d'un cas d'hépatite B chez un sujet non vacciné est de près de trois fois et demie celui d'un même cas chez un sujet vacciné n'ayant pas répondu au vaccin (US $711 contre US $207).

Les bénéfices totaux estimés résultant de la diminution de la morbidité seraient de US $68,8 millions, les coûts de US $36,7 millions, ce qui donne un rapport bénéfice/coût de 1,88:1 pour les seuls services de santé. Si l'on inclut également les bénéfices indirects dus à la diminution des absences au travail et de la mortalité, on arrive à un rapport bénéfice/coût de 2,77:1. Même si l'on exclut les bénéfices liés à la diminution du nombre de cancers et de transplantations du foie, ce rapport pour les seuls services de santé serait encore de 1,41:1.

Si l'on administre des rappels tous les 5 ans jusqu'à l'âge de 15 ans, le coût du programme augmentera de US $52,8 millions entre 1990 et 2034, abaissant ainsi le rapport direct bénéfice/coût à 1,31:1 et le rapport total bénéfice/coût à 2,58:1.

Suite à la mise en route du programme chez les 0 à 15 ans, il y aurait 384 000 cas d'hépatite B de moins entre 1990 et 2035. On pourrait obtenir cette diminution considérable de la morbidité sans aucun coût net pour la société; en fait, il s'ensuivrait une économie nette d'environ US $117,0 millions, dont environ US $32,3 millions pour les services de santé, ce qui suffirait à financer par exemple plus de 1300 transplantations rénales ou plus de 3700 pontages coronariens. L'adoption d'une telle politique de vaccination à l'échelon national semble donc justifiée non seulement sur le plan médical mais également sur le plan économique.

References

1. **Soberslavsky, O.** HBV as a global problem. In: Vyas, G.N. et al., ed. *Viral hepatitis*. Philadelphia, Franklin Institute Press, 1978, pp. 347–355.
2. **Hoofnagle, J.H. & Alter, H.** Chronic viral hepatitis. In: Vyas, G.N. et al., ed. *Viral hepatitis and liver disease*. New York, Grune & Stratton, 1984, pp. 97–113.
3. Hepatitis B vaccines prepared from yeast by recombinant DNA techniques: Memorandum from a WHO meeting. *Bulletin of the World Health Organization*, **63**: 57–61 (1985).
4. **Maynard, J.E. et al.** Control of hepatitis B by immunization: global perspectives. In: Zuckerman, A.J., ed. *Viral hepatitis and liver disease*. New York, Alan R. Liss, Inc., 1988, pp. 967–969.
5. **Gamen, D.** Persistent infection of humans with hepatitis B virus: mechanism and consequences. *Reviews of infectious diseases*, **4**: 1026–1047 (1982).
6. **Szmuzness, W.** Heptocellular carcinoma and the hepatitis B virus: evidence for a causal association. *Progress in medical virology*, **24**: 40–62 (1978).
7. **Maupas, P. & Melnick, J.L.** Hepatitis B infection and primary liver cancer. *Progress in medical virology*, **27**: 1–15 (1981).
8. **Beasley, R.P.** Hepatitis B virus as the etiologic agent in hepatocellular carcinoma: epidemiologic considerations. *Hepatology*, **2**: 21S–26S (1982).
9. **Prince, A.M. & Alcabes, P.** The risk of development of hepatocellular carcinoma in hepatitis B virus carriers in New York. A preliminary estimate using death-records matching. *Hepatology*, **2**: 15S–20S (1982).
10. **London, W.T.** Primary hepatocellular carcinoma: etiology, pathogenesis and prevention. *Human pathology*, **12**: 1085–1097 (1981).
11. **Nayak, N.C. et al.** Association of human hepatocellular carcinoma and cirrhosis with hepatitis B virus surface and core antigens in the liver. *International journal of cancer*, **20**: 643–654 (1977).
12. **Beasley, R.P. et al.** Hepatocellular carcinoma with HBV: a prospective study of 22 707 men in Taiwan. *Lancet*, **2**: 1129–1133 (1981).
13. **Tolsma, D.D. & Bryan, J.A.** The economic impact of viral hepatitis in the United States. *Public health reports*, **91** (4): 349–353 (1976).
14. Changing patterns of groups at high risk for hepatitis B in the United States. *Morbidity and mortality weekly report*, **37**: 429–437 (1988).
15. **Mulley, A.G. et al.** Indications for use of hepatitis B vaccine, based on cost-effectiveness analysis. *New England journal of medicine*, **307**: 644–652 (1982).
16. **Chemtob, D. et al.** Prevention strategy of hepatitis B virus infection among the Ethiopian community in Israel. *Israel journal of medical sciences*, **27**: 273–277 (1991).
17. **Adler, M. W. et al.** Should homosexuals be vaccinated against hepatitis B virus? Cost and benefit assessment. *British medical journal*, **286**: 1621–1624 (1983).
18. **Lahaye, D. et al.** Cost–benefit analysis of hepatitis B vaccination. *Lancet*, **2**: 441–443 (1987).

19. **Arevalo, J.A. & Washington, E.** Cost-effectiveness of prenatal screening and immunization for hepatitis B virus. *Journal of the American Medical Association*, **259**: 265–369 (1988).
20. *Statistical tables on selected infectious diseases 1971–1975*. Jerusalem, Central Bureau of Statistics, 1977 (Special Series No. 379).
21. *Statistical tables on selected infectious diseases 1976–1980*. Jerusalem, Central Bureau of Statistics, 1983 (Special Series No. 722).
22. *Statistical tables on selected infectious diseases 1981–1985*. Jerusalem, Central Bureau of Statistics, 1988 (Special Series No. 826).
23. *Statistical tables on selected infectious diseases 1986–1990*. Jerusalem, Central Bureau of Statistics (in press).
24. *Monthly epidemiological bulletin*, vol. 27, No. 1. Jerusalem, Ministry of Health January–March 1992, pp. 1–4.
25. **Polakoff, S. & Tillett, H.E.** Acute viral hepatitis B: laboratory reports 1975–79. *British medical journal*, **284**: 1881–1882 (1982).
26. **Green, M. et al.** Rise in the incidence of viral hepatitis in Israel in the face of improved socioeconomic conditions. *Reviews of infectious diseases*, **2**: 464–469 (1989).
27. **Reisler, D.M. et al.** Viral hepatitis in Israel: morbidity and mortality data. *American journal of epidemiology*, **92**: 62–72 (1970).
28. **Schwartz, T.A.** Epidemiology of hepatitis A in Israel. *Monographs in virology*, **15**: 53–58 (1984).
29. **Kark, J.D. & Bar Shani, S.** Hepatitis A antibody in Israel Defence Force recruits. *Journal of medical virology*, **6**: 341–345 (1981).
30. **Fattal, B.** Infectious disease morbidity in kibbutzim. *Harefuah*, **115**: 111–115 (1988).
31. **Eliakim, M.** Epidemiology of viral hepatitis in Israel, 1978. *Israel journal of medical sciences*, **15**: 248–255 (1979).
32. **Lange, W. & Mashi, K.N.** Epidemiologic and economic importance of hepatitis B in the Federal Republic of Germany. *Postgraduate medical journal*, **63** (suppl. 2): 21–26 (1987).
33. *Hospitalizations 1979*. Jerusalem, Central Bureau of Statistics, 1987 (Special Series No. 803).
34. *Hospitalizations 1976*. Jerusalem, Central Bureau of Statistics, 1983 (Special Series No. 708).
35. **Stewart, J.S. et al.** Three-year survey of viral hepatitis in West London. *Quarterly journal of medicine*, **47**: 365–384 (1978).
36. **Shalit, M. et al.** Non-A, non-B hepatitis not following transfusion: a study of hospital patients in Jerusalem. *Israel journal of medical sciences*, **18**: 986–987 (1982).
37. **Sandler, S.G. et al.** Seroepidemiology of hepatitis B virus in Israel. *American journal of epidemiology*, **106**: 76–82 (1977).
38. **Eshel, E. & Bassan, H.M.** Viral hepatitis types B and non-B. *Harefuah*, **96**: 180–182 (1979).
39. **Ben-Porath, E. et al.** Etiology of acute viral hepatitis in Israel. *Harefuah*, **108**: 583–585 (1985).
40. **Sandler, S.G. et al.** Type B and non-B viral hepatitis in Jerusalem. *Bulletin of the World Health Organization*, **54**: 193–197 (1976).
41. **Alkan, M. & Fainaru, M.** Etiology of hepatitis B antigen-positive acute viral hepatitis. *Harefuah*, **85**: 255–256 (1973).
42. **Krausz, Y. et al.** A comparative study of hepatitis B and non-B in hospitalized adults in an endemic area. *Israel journal of medical sciences*, **13**: 9–14 (1977).
43. **Szmuness, W. et al.** Hepatitis B vaccine; demonstration of efficacy in a controlled clinical trial in a high risk population in the United States. *New England journal of medicine*, **303**: 833–841 (1980).
44. **Francis, D.P. et al.** Prevention of hepatitis B with vaccine: report from the Centers for Disease Control multi-center efficacy trial among homosexual men. *Annals of internal medicine*, **97**: 362–366 (1982).
45. **Maupas, P. et al.** Efficacy of hepatitis B vaccine in prevention of early HBsAg carrier state in children: controlled trial in an endemic area (Senegal). *Lancet*, **1**: 289–292 (1981).
46. **Zu, Z.Y. et al.** Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. *Pediatrics*, **76**: 713–718 (1985).
47. **Ginsberg, G.M. & Shouval, D.** Cost–benefit analysis of a nationwide neonatal programme against hepatitis B in an area of intermediate endemicity. *Journal of epidemiology and community health*, (in press).
48. **Barbara, J.A.J. et al.** Indicators for hepatitis B immunoglobulin for neonates of HBsAg carrier mothers. *British medical journal*, **289**: 880 (1984).
49. **Mariner, E. et al.** Lack of perinatal transmission of hepatitis B virus infection in Senegal, West Africa. *Pediatrics*, **106**: 843–849 (1985).
50. **De Virgilis, S. et al.** Perinatal hepatitis B virus detection by hepatitis B virus DNA analysis. *Archives of disease in childhood*, **60**: 56–58 (1985).
51. **Greenfield, C. et al.** Perinatal transmission of hepatitis B virus in Kenya: its relation to the presence of serum HBV-DNA and anti-HBe in the mother. *Journal of medical virology*, **19**: 135–142 (1986).
52. **Hwang, L.U. et al.** Perinatal transmission of hepatitis B virus: role of maternal HBeAg and anti-HBc IgM. *Journal of medical virology*, **15**: 265–269 (1985).
53. **Naggan, L. et al.** Modes of transmission of hepatitis B infection in newborns and infants within the family (Abst.), In: Szmuness, W. et al., ed. *Viral Hepatitis and Liver Disease: Proceedings of an International Symposium in New York City*. Grune & Stratton, NY, 1981, pp. 670–671.
54. **Naggan, L. et al.** Prevalence of hepatitis B markers (HBsAg and HBsAb) in women screened at time of delivery. *Israel journal of medical sciences*, **16**: 347–350 (1980).
55. **Shouval, D. et al.** Study of 90 hepatitis B surface antigen carriers in Israel. *Israel journal of medical sciences*, **17**: 407–412 (1981).
56. **Dudley, F.J. et al.** Natural history of hepatitis-associated antigen-positive chronic liver disease. *Lancet*, **2**: 1388–1393 (1972).
57. **Tur-Kaspa, R. et al.** Detection and characteristics

of hepatitis B virus DNA in serum of HBe antigen-negative HBsAg carriers. *Journal of medical virology*, **14**: 17–26 (1986).
58. *Monthly bulletin of statistics,* vol. 41, No. 8. Jerusalem, Central Bureau of Statistics, August 1990, p. 4.
59. **Neuman, L. & Shemesh, A.** *The inoculated status of children before admission to first grade schools in 1990.* Jerusalem, Ministry of Health, December 1991.
60. **Szmuness, W. et al.** A controlled clinical trial of the efficacy of the hepatitis B vaccine: a final report. *Hepatology*, **1**: 377–385 (1981).
61. **Jonsson, B.** Cost–benefit analysis of hepatitis B vaccination. *Postgraduate medicine,* **63** (suppl. 2): 27–32 (1987).
62. **Stevens, C.E.** Perinatal hepatitis B virus transmission in the United States: prevention by passive–active immunization. *Journal of the American Medical Association*, **253**: 1740–1745 (1985).
63. **Beasley, R.P. et al.**. Hepatitis B immune globulin (HBIg) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state. *Lancet*, **2**: 383–393 (1981).
64. **Schwartz, J. S.** Hepatitis B vaccine. *Annals of internal medicine*, **100**: 149–150 (1984).
65. **Umenai, T. & Suzuki, H.** Hepatitis B vaccination. *World health*, 24–25 (November 1989).
66. **Ginsberg, G.M.** Cost–effectiveness analysis, cost–benefit analysis and the value of life in health care and prevention, In: Laaser, U. et al., ed. *Costs and benefits in health care and prevention.* Berlin, Springer-Verlag, 1990, pp. 6–19.
67. *Statistical abstract of Israel 1989.* Central Bureau of Statistics, Jerusalem, 1989.
68. **Zajac, B.A. et al.** Overview of clinical studies with HBV vaccine made by recombinant DNA. *Journal of infection*, **13** (suppl. A): 39–45 (1986).
69. **Andre, F.E.** Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *American journal of medicine*, **87** (suppl. 3A): 14S–20S (1989).
70. **Wainwright, R.B. et al.** Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. *Journal of the American Medical Association*, **261**: 2362–2366 (1989).
71. **McMahon, B.J. et al.** A comprehensive programme to reduce the incidence of hepatitis B viral infection and its sequelae in Alaskan natives. *Lancet*, **2**: 1134–1136 (1987).
72. **Beasley, R.P. et al.** Hepatitis B immune globulin (HBIg) for prevention of perinatal transmission of the HBV carrier state: final report of a randomized double-blind placebo-controlled trial. *Hepatology*, **3**: 135–141 (1983).
73. **Davidson, M. & Krugman, S.** Recombinant yeast hepatitis B vaccine compared with plasma dried vaccine: immunogenicity and effect of a booster dose. *Journal of infection,* **13** (suppl. A): 31–38 (1986).
74. **Beasley, R.P. et al.** Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet*, **2**: 1099–1102 (1983).
75. **Bogomolski-Yahalom, V. et al.** Prevalence of HBsAg carriers in native and immigrant pregnant female populations in Israel and passive/active vaccination against HBV of newborns at risk. *Journal of medical virology*, **34**: 217–222 (1991).
76. **Kane, M.A. et al.** Routine prenatal screening for hepatitis B surface antigen. *Journal of the American Medical Association*, **259**: 408–409 (1988).
77. **Alter, M.J. et al.** Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. *Journal of the American Medical Association*, **262**: 1201–1205 (1989).
78. **Ben-Porath, E. et al.** Hepatitis B virus infection and liver disease in Ethiopian immigrants to Israel. *Hepatology*, **1**: 662–666 (1987).
79. **Egoz, N. et al.** Prevalence of hepatitis B antigen among army inductees. *Israel journal of medical sciences*, **1**: 777–780 (1975).
80. **Berger, S.A. et al.** A benefit–cost analysis of routine mumps and rubella vaccination for Israeli infants. *Israel journal of medical sciences*, **26**: 74–80 (1990).
81. **Ginsberg, G.M. & Tulchinsky, T.H.** Costs and benefits of a second measles innoculation in Israel, the West Bank, and Gaza. *Journal of epidemiology and community health*, **44**: 274–280 (1990).
82. **Tulchinsky, T.H. et al.** Measles in Israel, the West Bank and Gaza: incidence and the case for a new eradication strategy. *Reviews of infectious diseases*, **12**: 951–958 (1990).